

Amendment and Response*Serial No.: 09/847,670**Confirmation No.: 4815**Filed: May 2, 2001**For: HEPATITIS C VIRUS HELICASE CRYSTALS, CRYSTALLOGRAPHIC STRUCTURE AND METHODS*

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Remarks

The Office Action mailed July 16, 2003 has been received and reviewed. Claims 50-59 having been added and claims 39, 41, and 49 having been amended, the pending claims are claims 31-43 and 47-59.

Claims 39, 41, and 49 have been cosmetically amended to recite that "the Hepatitis C virus helicase" (i.e., the claimed crystalline Hepatitis C virus helicase) is SEQ ID NO:1.

New claims 50 and 52 are supported, for example, by originally filed claims 39 and 41. New claim 51 is supported by the specification at, for example, page 29, lines 25-30. New claims 53 and 54 are supported, for example, by originally filed claims 38 and 40, respectively. New claims 55-57 are supported by the specification at, for example, page 9, lines 11-22. New claims 58 and 59 are supported, for example, by originally filed claims 31 and 35, respectively.

Reconsideration and withdrawal of the rejections are respectfully requested.

Objection to the Title

The Examiner objected to the title for reciting "methods," noting that the elected claims do not contain methods. Applicants note that although method claims (e.g., claims 31-37 and 47-48) have been withdrawn from consideration by the Examiner, they remain pending, and Applicants are requesting, herein below, that the Examiner reconsider the restriction requirement and/or rejoin the non-elected method claims upon allowance of any of the elected product claims.

If necessary, Applicants will provide an appropriate amendment to the title upon notification of allowable subject matter.

Rejection under 35 U.S.C. §112, Second Paragraph

The Examiner rejected claims 39, 41, 43, and 49 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject

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matter which Applicants regard as the invention. Specifically, the Examiner alleged that claims 39, 41, and 49 (and dependent claim 43) are vague and indefinite because it is not clear whether the sequence is referring to the entire sequence or just a fragment of the sequence. Applicants respectfully traverse the rejection.

Applicants respectfully submit that the claims clearly and distinctly convey the claimed invention to one of skill in the art. Specifically, claims 39, 41, and 49 (as amended) each recite that the amino acid sequence of the Hepatitis C virus helicase (i.e., the claimed crystalline Hepatitis C virus helicase) *is* SEQ ID NO:1 (emphasis added).

"[T]he sequence rules define a set of symbols and procedures that are both mandatory and the only way that an applicant is permitted to describe information about a sequence that falls within the definitions used in the rules." (M.P.E.P. §2421.02). "37 CFR 1.821(c) requires that each sequence disclosed in the application appear separately in the 'Sequence Listing,' with each sequence further being assigned a sequence identification number, referred to as 'SEQ ID NO.' " (M.P.E.P. §2422.03). Thus, SEQ ID NO:1 is the symbol required by the rules to be used by Applicants to refer to the 473 amino acid protein sequence that is described in the present Sequence Listing as SEQ ID NO:1. Thus, the recitation that "the amino acid sequence of the Hepatitis C virus helicase *is* SEQ ID NO:1" (e.g., claims 39, 41, and 49, as amended) necessarily means that the amino acid sequence of the Hepatitis C virus helicase is the entire 473 amino acid protein sequence that is described in the present Sequence Listing as SEQ ID NO:1. Further, Applicants hereby affirmatively state on the record that they are **not claiming** (e.g., in claims 39, 41, and 49) crystalline Hepatitis C virus helicase wherein the amino acid sequence of the Hepatitis C virus helicase is a **fragment of SEQ ID NO:1**.

Applicants respectfully request that the Examiner reconsider and withdraw the rejections under 35 U.S.C. §112, second paragraph.

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Rejection under 35 U.S.C. §112, First Paragraph***Rejection for Lack of Enablement***

The Examiner rejected claims 42, 43, and 49 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the Examiner acknowledged that the specification provides enablement for making crystals of crystalline Hepatitis C virus helicase with unit cell dimensions of $a = b = 109 \text{ \AA} \pm 3 \text{ \AA}$; $c = 84 \text{ \AA} \pm 2 \text{ \AA}$; $\alpha = \beta = \gamma = 90^\circ$; and space group P4₁; as well as $a = 66 \text{ \AA} \pm 2 \text{ \AA}$; $b = 110 \text{ \AA} \pm 3 \text{ \AA}$; $c = 64 \text{ \AA} \pm 2 \text{ \AA}$; $\alpha = \beta = \gamma = 90^\circ$; and a space group P2₁2₁2₁; but alleged that the specification does not reasonably provide enablement for other crystalline Hepatitis C virus helicases and compositions including the same. Applicants respectfully traverse the rejection.

"A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." M.P.E.P. §2164.04. "As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied." M.P.E.P. §2164.01(b). "For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be *used* in that manner without undue experimentation. Proof of enablement will be required for other members of the claimed genus only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not *use* the genus as a whole without undue experimentation." M.P.E.P. §2164.02, paragraph entitled "WORKING

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EXAMPLES AND A CLAIMED GENUS" (emphasis added). "[E]ven in unpredictable arts, a disclosure of every operable species is not required." M.P.E.P. §2164.03.

The specification clearly defines the protein to be crystallized as being Hepatitis C virus helicase having amino acid sequence SEQ ID NO:1 (e.g., Figure 2 and claims 37, 39, and 41-42). The specification clearly describes methods of crystallizing Hepatitis C virus helicase having amino acid sequence SEQ ID NO:1 (e.g., page 11, line 21 to page 12, line 12, and claims 31 and 35). Although not required, and as admitted by the Examiner, Applicants have even provided working examples of making two different crystals (e.g., having different space groups and different cell dimensions) of Hepatitis C virus helicase having amino acid sequence SEQ ID NO:1 (e.g., page 39, line 28 to page 41, line 7). Further, the specification provides methods of using crystals of Hepatitis C virus helicase having amino acid sequence SEQ ID NO:1 including, for example solving crystal structures (e.g., pages 12-17) and incorporating a chemical entity in a crystal (e.g., claims 47-48). Notably, the Examiner has not provided any reason to doubt the objective truth of the disclosure provided in the specification.

Further, Applicants respectfully submit that one of skill in the art, using the disclosure provided in the specification (including the working examples), would be able to make and use the entire scope of the invention as recited in claims 42, 43, and 49. For example, Applicants' disclosure of methods of making and using two different crystals of Hepatitis C virus helicase having amino acid sequence SEQ ID NO:1 may provide tools for one of skill in the art, without undue experimentation, to make additional crystals of Hepatitis C virus helicase having amino acid sequence SEQ ID NO:1. For example, one of skill in the art might use the presently disclosed crystals in, for example, cross-seeding techniques (see the specification at, for example, page 39, line 29, and page 40, lines 2 and 23-24, for disclosure of seeding) to make additional crystals of Hepatitis C virus helicase having amino acid sequence SEQ ID NO:1.

Moreover, the specification discloses working examples of compositions including crystalline Hepatitis C virus helicase having amino acid sequence SEQ ID NO:1 (e.g., claim 43). In addition to Hepatitis C virus helicase having amino acid sequence SEQ ID NO:1, the disclosed compositions include, for example, water, dimethyl sulfoxide, glycerol,

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polyethylene glycols, polyethylene glycol monoethers, salts, buffers, and combinations thereof (e.g., crystals in cryogenic solutions as described, for example, in the specification at page 40, lines 25-26; page 41, lines 8-17 and 26-28). Notably, Applicants are not claiming co-crystals or liganded complexes (e.g., claims 38-43), and the claimed compositions do not require chemical entities or ligands as suggested by the Examiner.

Thus, Applicants respectfully submit that claims 42, 43, and 49 are fully enabled by the specification.

Rejection for Lack of Written Description

The Examiner rejected claims 38-43 and 49 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

First, the Examiner noted that some of the present claims recite open claim language (e.g., "comprising" and "having") such that the crystalline Hepatitis C virus helicase might include other crystals that do not meet the written description provision of 35 U.S.C. §112, first paragraph. Applicants respectfully traverse the rejection.

Applicants agree that some of the present claims do use open claim language, which means that the crystalline Hepatitis C virus helicase must include the subject matter described in the claim, and may optionally include additional subject matter (e.g., other crystals). The Examiner has not provided any convincing reasons or rationale as to why the subject matter described in the claims does not meet the written description provision of 35 U.S.C. §112, first paragraph, but instead has chosen to focus on *lack of written description for what is not recited in the claims*. Thus, Applicants respectfully submit that the rejection is not a written description rejection to the subject matter described in the claims, but a rejection to the use of "comprising" and "having" as transitional phrases. Applicants respectfully traverse the rejection and submit that the use of "comprising" or "having" as a transitional phrase is proper and is even acknowledged by the M.P.E.P. (*see, for example*, M.P.E.P. §2111.03).

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Second, regarding claims 39, 41, 42, and 49 (and dependent claim 43), the Examiner asserted that the amino acid sequence may contain the entire sequence or "just a fragment of the sequence." Applicants respectfully disagree. As described herein above, SEQ ID NO:1 is the symbol required by the rules to be used by Applicants to refer to the 473 amino acid protein sequence that is described in the present Sequence Listing as SEQ ID NO:1. Thus, the recitation of "SEQ ID NO:1," necessarily refers to the entire 473 amino acid protein sequence that is described in the present Sequence Listing as SEQ ID NO:1.

Finally, the Examiner repeatedly refers to "SEQ ID NO:1 and its complement of the same length" as meeting the written description provisions of 35 U.S.C. §112, first paragraph. Applicants respectfully note that SEQ ID NO:1 is an amino acid sequence. Applicants' Representatives are unaware that amino acid sequences (e.g., SEQ ID NO:1) have complements. Clarification of the Examiner's remarks in the next Official Communication is respectfully requested.

Based on the remarks presented herein above, Applicants respectfully request that the Examiner reconsider and withdraw the rejections under 35 U.S.C. §112, first paragraph.

Rejection under 35 U.S.C. §102

The Examiner rejected claims 42, 43, and 49 under 35 U.S.C. §102(b) as being anticipated by Kim et al. ("Hepatitis C Virus NS3 RNA Helicase Domain with a Bound Oligonucleotide: The Crystal Structure Provides Insights into the Mode of Unwinding," *Structure*. 1998;6(1):89-100). Applicants respectfully traverse the rejection.

Claim 42 recites "[c]rystalline Hepatitis C virus helicase having amino acid sequence SEQ ID NO:1," and claim 49 (as amended) recites that "the amino acid sequence of the Hepatitis C virus helicase is SEQ ID NO:1." Claim 43 depends from claim 42. As described herein above, SEQ ID NO:1 is the symbol required by the rules to be used by Applicants to refer to the 473 amino acid protein sequence that is described in the present Sequence Listing as SEQ ID NO:1. Thus, the recitation of "SEQ ID NO:1" necessarily refers to the entire 473 amino acid protein sequence that is described in the present Sequence Listing as SEQ ID NO:1.

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Kim et al. fails to disclose or suggest, among other things, a crystal that includes the entire 473 amino acid protein sequence that is described in the present Sequence Listing as SEQ ID NO:1. Thus, Applicants respectfully submit that claims 42, 43, and 49 are not anticipated by Kim et al. Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. §102.

New Claims

Applicants respectfully submit that new claims 50-59 are patentable for reasons similar to those presented herein above for the patentability of claims 38-43 and 49. Applicants respectfully request that the Examiner enter, consider, and pass new claims 50-59 on to allowance.

Request for Interview

Applicants thank the Examiner for issuing the present Official Communication as a second non-final Office Action. In the event that the next Official Communication is not a Notice of Allowance, Applicants' Representatives hereby respectfully request a telephonic interview with the Examiner and the Supervisory Patent Examiner to discuss any remaining issues.

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It is respectfully submitted that all the pending claims are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted for
Finzel et al.

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October 16, 2003

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CERTIFICATE UNDER 37 CFR §1.8:

The undersigned hereby certifies that the Transmittal Letter and the paper(s), as described hereinabove, are being transmitted by facsimile in accordance with 37 CFR §1.6(d) to the Patent and Trademark Office, addressed to Assistant Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 16 day of OCTOBER, 2003, at 1:22 pm (Central Time).

By: 
Name: SAM HER